Applicants : BERMUDES, et al.
U.S. Serial No.: 10/790,586
Filed : March 1, 2004
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REMARKS

Applicants have amended the value, "17", in Table 2B on page 45, line 18, of the originally-filed specification to reflect the correct value of "1.7". The error is inadvertent and of a clerical nature. Applicants respectfully request that Examiner enter this amendment.

Objections

The Examiner objected to the specification on grounds that "the page numbers on the Table of Contents pages are separate and not consecutive with those of the remainder of the specification."

In response, Applicants have deleted the Table of Contents, thus rendering this ground of objection moot. Accordingly, Applicants respectfully request the Examiner to withdraw this ground of objection.

35 U.S.C. 112, 1st Paragraph Rejection (Enablement)

The Examiner rejected claims 25-43 under 35 U.S.C. 112, 1st paragraph, on grounds that "the specification, while enabling for particular tumor targeting Salmonella strains, and a method [f]or using said strain, does not reasonably provide enablement for any tumor-targeting Salmonella strain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims."

In formulating this rejection, the Examiner considered the following factors from In re Wands, 858 F.2d 731, 8 USPQ2d 1400

(Fed. Cir 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Breadth of the claims

The Examiner states that "[t]he present claims are very broad."

In response, Applicants neither refute nor concur with this conclusion but would like to note that claim breadth, alone, is insufficient to render a claim non-enabling.

Nature of the invention

The Examiner states that "[t]he nature of the invention is a composition comprising a tumor-targeting Salmonella bacterium containing an F' pilus and bacteriophage, and a method of delivering bacteriophage to solid tumors."

Applicants would like to emphasize that the present invention is directed to Salmonella which can directly deliver *bacteriophage* to tumors in high numbers.

State of the prior art

The Examiner states that "the state of the art suggests that use of bacteria as a vehicle for transferring heterologous nucleotide sequences to eukaryotic cells of an animal is undeveloped, inefficient, and unpredictable."

In response, the analysis of the prior art by the Examiner is directed towards bacteria as *DNA* delivery systems to mammalian cells. Although Applicants believe that DNA delivery to mammalian cells is within the scope of the present invention, the pending claims are not directed towards DNA delivery, but rather, to the delivery of the *phage* themselves. In Applicants' December 8, 2004 response, Applicants specifically pointed out that the claims were amended to remove the language, "gene of interest." Applicants directed the then new claims toward delivery of the entire phage, which are a combination of the phage DNA and the phage protein, including the phage coat proteins. Prior art is described below where delivery of phage and their modified coat proteins is an area of interest and is an inefficient process which is greatly improved by using the present invention.

Phage delivery to tumors is useful in the discovery of peptide ligands fused to the phage coat. Filamentous phage have documented use in cancer diagnostic and therapeutic discovery (e.g., Pasqualini, et al., 1997; Figini, et al., 1998). None of the prior art provides a methodology for the delivery of filamentous phage directly to tumors in high numbers by intravenous administration. For example, Pasqualini, et al., (1997) demonstrated approximately 2×10^3/mg or 2×10^6/g (Figure 1) phage within tumors; only a two-fold increase compared to brain or kidney (based on total phage rather than comparison of purification from the library). From these phage, novel peptide ligands were able to be recovered, however, because the number of phage reisolated was low, the number of potential peptide ligands was limited. Delivery directly to tumors by

intravenously-administered attenuated, tumor-targeted *Salmonella* is novel and as is the method for delivering phage to tumors in high numbers.

Relative skill of those in the art

The Examiner states that "[t]he relative skill of those in the art of recombinant DNA techniques and microbiology is high. The relative skill of those in the art of gene therapy and treatment of solid tumors using gene therapy is low."

In response, the method for making the phage-expressing bacteria utilizing basic microbiology procedures can be readily understood by those skilled in the art, in light of Applicants' disclosure, including: 1) transfer of an F' by mating (see Methods of Enzymology 1991, Vol. 204: 43-62), 2) selection for the F' on the appropriate media (lac-), 3) introduction of the phage by infection, and 4) selection of the phage-infected cells by plating to kanamycin. Tumor-targeting strains of Salmonella are available from the American Type Culture Collection (ATCC).

Predictability or unpredictability of the art

The Examiner states that "the method of gene therapy[,] in general, and the use of bacteria as delivery systems to eukaryotic cells in vivo[,] in particular, is highly complex and unpredictable[,] and the skilled artisan[,] at the time of the present invention was made[,] recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the effectiveness of a potential new delivery system, such as tumor-targeted bacteria containing a

bacteriophage, cannot be predicted in the absence of in vivo testing."

In response, as discussed supra, Applicants note that the Examiner's conclusion is based on DNA delivery, rather than the delivery of the *phage* themselves. Accordingly, Applicants respectfully request reconsideration of the Examiner's conclusion in light of the arguments presented herein.

Amount of direction or guidance presented

The Examiner states that "[t]he present specification provides little direction or guidance to support the claimed invention." The Examiner additionally states that it is "not clear what causes any tumor-targeting of the Salmonella strains in Example 6 of the specification" and "thus it is unclear if one could readily generate such tumor[-]targeting in other Salmonella strains or serotypes, unless it is an inherent property of all Salmonella."

In response, Applicants note that Pawelek, et al., 1997 Cancer Research 57: 4537-4544, teaches that both wild type and attenuated strains are capable of targeting tumors. Six strains were demonstrated to target tumors, including the wild type, and therefore it is an inherent property of Salmonella. Low, et al., 1999 Nature Biotechnology, further demonstrated that multiple strains of lipid mutant (strains with disruptions of the msbB gene) Salmonella were able to target tumors.

In Example 6, the only selections are 1) for lac+ Salmonella (Salmonella are lac- and therefore can be selected for on plates

containing lactose) and 2) for Kanamycin resistance. It can be appreciated by those skilled in the art that the phage used, M13KO7, is a M13 phage carrying a kanamycin reistance gene. Selection for strains with kanamycin resistance thereby select for strains carrying the phage. As described supra, the method for making the phage-expressing bacteria utilizing basic microbiology procedures will be readily understood by those skilled in the art, in light of Applicants' disclosure, including 1) transfer of an F' by mating, 2) selection for the F' on the appropriate media (lac-), 3) introduction of the phage by infection, and 4) selection of the phage-infected cells by plating to kanamycin. Tumor-targeting strains of Salmonella are available from the American Type Culture Collection (ATCC).

Presence or absence of working examples of the invention

The Examiner states that "[a]n example is disclosed wherein particular Salmonella expressing F' pilus are infected with a phagemid in which the gene of interest is green fluorescent protein (GFP) and are used to infect mammalian M2 cells. Expression of GFP is shown. Another example discloses injecting mice containing melanoma tumors with particular Salmonella that are expressing F' pilus and are infected with filamentous phage M13KO7. Tumor and liver homogenates and supernatants are compared for the presence of bacteria and the presence of phage."

In response, Applicants note that examples illustrating the present invention are shown on pages 42-49 of the specification. In the present application, lipid mutants (msbB- strains YS1646 and YS1456) and a non-lipid mutant (YS72) were used. Methods to

introduce the F' in one step based upon selection for lac+ Salmonella were described. It is well-known to those skilled in the arts that *Salmonella* is a lac- organism, and therefore selection for lac+ is universally applicable. The introduction of the phage in a second step can be readily appreciated by those skilled in the art and would be universally applicable with filamentous phage which recognize the F' (male) pilus (since *Salmonella* is a lac- organism). Accordingly, Applicants maintain that those ordinarily-skilled in the art will appreciate the full scope of Applicants' disclosure as applied to *Salmonella*.

Quantity of experimentation necessary

The Examiner states that "[t]he quantity of experimentation necessary to carry out the claimed invention is high since the skilled artisan could not rely on the prior art of the present specification to teach how to use the claimed method."

In response, and as described supra, the method for making the phage-expressing bacteria utilizing basic microbiology procedures can be readily-appreciated by those skilled in the art, in light of Applicant' disclosure, including 1) transfer of an F' by mating, 2) selection for the F' on the appropriate media (lac-), 3) introduction of the phage by infection, and 4) selection of the phage-infected cells by plating to kanamycin. Tumor-targeting strains of Salmonella are available from the American Type Culture Collection (ATCC). The methods for introducing the bacteria by intravenous, intraperitoneal, or intratumoral injection may be by syringe/needle injection, as described by the earlier-mentioned publication, Pawelek, et al.

Pursuant to the Examiner's suggestions and to facilitate the prosecution of the present application, Applicants have amended the claims to better reflect the subject matter illustrated by the examples in the specification. To aid the amendment process, Applicants have canceled claims 25-43, without prejudice to Applicants' right to subsequently pursue the canceled subject matter in the present or future application, thus rendering this ground of rejection moot. Additionally, Applicants have added new claims 44-63 which are derived from canceled claims 25-43, with particular focus on the examples disclosed in the specification. Applicants maintain that new claims 44-63 are well-supported by the specification and do not contain new matter.

In particular, new claim 44 is derived from canceled claim 25, and is additionally supported, for instance, by page 7, lines 14-15, of the originally-filed specification.

Support for new claim 45 may be found, for instance, on page 9, lines 13-15, of the originally-filed specification.

Support for new claim 46 may be found on page 9, line 15, and on page 42, line 24 (reference to *Salmonella* strain 72 in WO 96/40238), of the originally-filed specification. With regard to WO 96/40238, support may be found, for instance, on page 147, line 7.

Support for new claim 47 may be found, for instance, on page 17, line 33, to page 18, line 6, of the originally-filed specification.

Support for new claim 48 may be found, for instance, on page 44, line 28, of the originally-filed specification.

Support for new claim 49 may be found, for instance, on page 10, lines 16-21, and on page 42, lines 24 and 34, of the originally-filed specification and on page 147, line 7, of WO 96/40238 (which is referenced on page 42, line 24, of the originally-filed specification).

Support for new claim 50 may be found, for instance, on page 43, lines 1-3, and on page 45, line 33, of the originally-filed specification.

Support for new claim 51 may be found, for instance, in Examples 6.2-6.4 of the originally-filed specification.

Support for new claims 52 and 53 may be found, for instance, on page 45, lines 19 and 22, of the originally-filed specification.

Support for new claim 54 may be found, for instance, on page 27, line 19, of the originally-filed specification.

Support for new claim 55 may be found, for instance, on page 43, line 14; page 45, line 33; and page 47, line 9, of the originally-filed specification.

Support for new claim 56 may be found, for instance, on page 12, line 11, of the originally-filed specification.

Support for new claim 57 may be found, for instance, on page 42, line 12, of the originally-filed specification.

Support for new claims 58 may be found, for instance, on page 42, line 29, and on page 43, lines 2-3, of the originally-filed specification.

Support for new claim 59 may be found, for instance, on page 43, line 2, and on page 44, line 35, of the originally-filed specification.

Support for new claim 60 may be found, for instance, on page 9, lines 3-9, of the originally-filed specification.

Support for new claim 61 may be found, for instance, on page 7, lines 25-35, of the originally-filed specification.

Support for new claim 62 may be found, for instance, on page 41, lines 18-31, of the originally-filed specification.

Accordingly, Applicants respectfully request the Examiner to withdraw this ground of rejection.

35 U.S.C. 112, 1st Paragraph Rejection (Written Description)

The Examiner rejected claims 25-43 under 35 U.S.C. 112, 1st paragraph, on grounds of "failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

In response, Applicants note that the Examiner's concerns are similar to those discussed in the previous section. Thus, pursuant to the Examiner's suggestions and to facilitate the prosecution of the present application, Applicants have amended the claims to better reflect the subject matter illustrated by the examples in the specification. As noted supra, to aid the amendment process, Applicants have canceled claims 25-43, without prejudice to Applicants' right to subsequently pursue the canceled subject matter in the present or future application, thus rendering this ground of rejection moot. Additionally, Applicants have added new claims 44-63 which are derived from canceled claims 25-43, with particular focus on the examples disclosed in the specification. Applicants maintain that new claims 44-63 are well-supported by the specification and do not contain new matter.

Accordingly, Applicants respectfully request that the Examiner withdraw this ground of rejection.

35 U.S.C. 112, 2nd Paragraph Rejection

The Examiner rejected claims 25-43 under 35 U.S.C. 112, 2nd paragraph, on grounds of being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner states that "[c]laims 25, 26, 40-43 and by dependence, claims 27-39 are vague and indefinite in the recitation of '. . . capable of . . .', since this

phrase refers to a latent ability, and it is unknown whether the ability is expressed or observed in the invention."

In response, Applicants have amended the claims to remove the offending language, "capable of."

Accordingly, Applicants respectfully request the Examiner to withdraw this ground of rejection.

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If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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